Reviewer's report

Title: Investigation of idiopathic versus connective tissue disease associated nonspecific Interstitial Pneumonia

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Reviewer: VERA LUIZA CAPELOZZI

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Major Compulsory Revisions

Is the question posed by the authors well defined?

The authors start from the premise that NSIP, even diagnosed as idiopathic NSIP initially, might be associated with an autoimmune background that later reveals itself as an organ-specific or a systemic autoimmune disease. Their premise gain support in the previous literature where in a cohort study of 27 idiopathic NSIP patients, above 50% cases developed an autoimmune disease after a mean follow-up of 22 months. Another study revealed that CTD developed in 10% of idiopathic NSIP during a period of follow-up. It is suggested that NSIP should be considered as a provisional clinical diagnosis and further study is recommended for characterizing of this condition. They also referred that current literatures are controversial in terms of prognosis between patients with idiopathic NSIP and CVD-NSIP.

Based on the premise that CTD-NSIP is similar to i-NSIP on clinical and radiologic features, no difference in disease outcome, they question if it is worth to distinguish CTD-NSIP from i-NSIP.#

To answer this question, they reviewed the clinical, radiologic and physiologic findings in NSIP patients with CTD and i-NSIP in their Institution.

2. Are the methods appropriate and well described?

The authors reported 354 cases that underwent surgical lung biopsy in the last 10 years at their Institution, but didn’t mention the clinical suspicion for these cases: diffuse infiltrates? IPF? OP? NSIP?

According to them, 101 cases were diagnosed as NSIP, but 4 cases drug-induced were excluded, but didn’t mention how many cases were excluded because airborne antigen or environmental exposures.

They included 97 cases in the study and their clinical features, radiological images and histopathology were reviewed and analyzed. With respect to the histopathology, they used the criteria proposed by ATS/ERS 2002, instead of the recent update of the International Multidisciplinary Classification of the Idiopathic Interstitial Pneumonias published in Am J Respir Crit Care Me 188: 733-748, 2013. According to this new statement it was recommended that NSIP be accepted as a distinct entity among the IIPs, with removal of the term
“provisional”. Importantly, NSIP pattern occurs not only as an idiopathic condition, but also in a variety of settings including CVD, hypersensitivity pneumonitis, drug toxicity, and some patients with familial pulmonary fibrosis. So, my question is, the final diagnosis included Multidisciplinary Discussion? What was the more predominant pattern? Fibrotic? Cellular pattern is more rare, but the authors report in Table 4 that they found almost 60% of the cases. In these cellular cases, a differential diagnosis with lymphoid interstitial pneumonia (LIP) was considered? Usually, organizing pneumonia (OP) is associated with NSIP and rarely inconspicuous honeycomb. Did these patterns were seen in the cases included in the study. It should be remembered that the presence of OP or honeycomb may influence the progress of the disease and thus the prognosis. I suggest to the authors compose a panel with clear examples of the more important histologic parameters found by the pathologist during the review of the cases.

They included BAL in the Methods but no mentions of the analysis are reported in the Results section.

The Tables should be re-constructed because are not self-explanatory, include several abbreviations with no meaning in the bottom and include two rows of results for each parameters difficult to interpret (see Table 4). In addition, they should include in the bottom the statistical method employed and the main results obtained.

The authors reported in the Statistical Analysis that Cox Regression was employed to evaluate risk factor for survival, but in Results section the obtained model controlled for all the variables included in the study are not shown. For example, important variables, such as fibrotic or cellular pattern of NSIP, smoking status, pulmonary function tests should be controlled in the Cox regression to obtain the real risk of death.

To answer questions 3 to 6 it is necessary to deal with the observations made in Methodology.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
To answer this question it is necessary to deal with the observations made in Methodology.

5. Are the discussion and conclusions well balanced and adequately supported by the data?
No

6. Are limitations of the work clearly stated?
No

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
No

8. Do the title and abstract accurately convey what has been found?
No
9. Is the writing acceptable?
No, the English language should be reviewed by a native professional.

**Level of interest:** An article of limited interest

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I declare that I have no competing interest